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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/565,616	06/09/2006	Zee Upton	FAK8011	2998
26294 7590 05/26/2010 TAROLLI, SUNDHEIM, COVELL & TUMMINO L.L.P. 1300 EAST NINTH STREET, SUITE 1700 CLEVELAND, OH 44114				
EXAMINER				
SGAGIAS, MAGDALENE K				
ART UNIT		PAPER NUMBER		
1632				
MAIL DATE		DELIVERY MODE		
05/26/2010		PAPER		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/565,616

Applicant(s)

UPTON ET AL

Examiner

Magdalene K. Sgagias

Art Unit

1632

Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 March 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-28 and 35-38 is/are pending in the application.
- 4a) Of the above claim(s) 3, 4, 6, 8-20, 24-28, 35 and 36 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 2, 5, 7, 21-23, 37 and 38 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 24 January 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsman's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 05/07/2010
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/22/2010 has been entered.

Applicant's arguments filed 03/22/2010 have been fully considered. Claims **1-28, 35-38** are pending. The amendment has been entered. Claims **29-34** are canceled. Claims **3-4, 6, 8-20, 24-28, 35-36** are withdrawn. Claims **1-2, 5, 7, 21-23, 37-38** are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim recites the phrase " other than IGF-I/vitronectin (VN) synthetic chimera". It is not clear what comprises the metes and bounds of a synthetic chimera.

Claim Rejections - 35 USC § 112/Necessitated by amendment

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims **1-2, 5, 7, 21-23, 37** under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the amendment.

Claims **1-2, 5, 7, 21-23, 37-38** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

37 CFR 1.118(a) states "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application". In the instant case, the recitation of limitation... "Wherein when said IGF-I is present other than as an IGF-I/vitronectin (VN) synthetic chimera....." (claim 1) is considered new matter. Applicants introduced said amendment filed on 02/13/2009. However, upon further review of the instant specification, examiner could not find support for such negative limitation. Furthermore, the specification lacks any description of such negative limitation as recited in the claim 1.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph-written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981) teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time application was filed...If a claim is amended to include subject matter, limitation or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the

examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes, "When an amendment is filed in reply to an objection or rejection based on U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendment made to the disclosure".

To the extent the claimed compositions are not described in the instant disclosure, claims **1-2, 5, 7, 21-23, 37-38** are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since the applicants disclosure do not teach a composition that is adequately described in the specification. In this case, it appears that the claims reflect a genus of IGF-I is present other than as an IGF-I/vitronectin (VN) synthetic chimera. The claims as amended lack functional negative characteristics that is the mammalian culture medium IGF-I is present other than as an IGF-I/vitronectin (VN) synthetic chimera. A review of art would indicate that many mammalian cell culture media comprise IGF-I is present other than as an IGF-I/vitronectin (VN) synthetic chimera, however it is clearly not an IGF-I. Simply providing, for what the culture medium does not have would constitute an enormous amount of experimentation to empirically test all these mammalian culture media to determine if they comprise IGF-I present other than as an IGF-I/vitronectin (VN) synthetic chimera. As described before, the specification does not provide guidance on determining what is included or excluded by the claims as amended and therefore an artisan of skill would require undue experimentation to practice or make and/or use the invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-2, 5, 7, 21-23, 37-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Upton et al** [WO 02/24219 (IDS)]; **Vuori et. al.** (US Pat. No. 5,830,504, 1998); **Sommer et al**, (US Pat. No. 5,407,913, 1995); in view of **Klemke et al**, (The Journal of Cell Biology, 127: 859-866, 1994); **Nam et al** (Endocrinology, 143(1): 30-36, 2002).

Upton (WO 02/24219)discloses a mammalian cell culture system of human keratinocytes, wherein the medium is comprised of (i) IGF-I (p 38, claim 10); (ii) vitronectin (p 38, claim 8); (iii) absence of serum. Upton teaches the culture medium further contains IGFBP3 (p 38, claim 23). Upton teaches the cultured keratinocytes can be used to augment or diminish binding between IGFs, IGFBPs and vitronectin in vitro with a view to manipulating contingent in vivo biological events associated with cell growth, proliferation and migration are suppressed such as for the purposes of wounds prone to hypertrophic scarring (abstract). Upton discloses the binding assays of IGF-I to vitronectin in the presence of recombinant IGFBP3 in the absence of serum (example 4, pages 28-29). Upton et al discloses the absence of serum as evidenced by the reference by incorporation in example 4, binding studies [see Upton et al (Comparative Biochemistry and Physiology Part B, 121: 35-41, 1998, page 37, 2nd column, under section, 2.3.2 IGF binding studies). Upton discloses the culture of the keratinocytes on a culture vessel, following pre-binding of IGF-I to vitronectin in culture dishes, cells were seeded into the wells (pages 28-29).

Vuori et al, supplements the teachings of Upton by teaching a recombinant protein complex comprising the growth factor IGF-I, an IGFBP3 and vitronectin, and a pharmaceutical composition comprising the isolated protein complex. Vuori et.al, teach that a protein complex of an insulin-like growth factor (IGF) and vitronectin enhance cell growth and tissue generation in a synergistic manner (column 4, line1-12). Further, they teach that the pharmaceutical composition comprising IGF and vitronectin promotes wound healing and tissue regeneration (column 2, line 15-29). **Sommer et al**, teach that a protein complex comprising a native or recombinant IGF and an insulin-like growth factor binding protein (IGFBP) enhances systemic tissue repair and healing in burn injuries (column 5, line 35-42, and line 65 continued through column 6, line 3). Further, Sommer et al teach making a composition of IGF-I and IGFBP-3 by mixing two together in equimolar amounts in a phosphate buffered saline or normal saline solution. Sommer et al also teach that IGF comprises IGF-I and IGF-II (column 4 line 62-64), and IGF binding protein is of IGFBP3.

Upton taken with Vuori taken with Sommer does not teach a vitronectin binding to the αv integrin receptor.

However, at the time of the instant invention **Klemke et al** teaches that receptor tyrosine kinase signaling required for integrin $\alpha v \beta 5$ -directed cell motility but not adhesion on vitronectin (title). Klemke teaches that for wound repair the adhesive interactions between the cells and the extracellular matrix are mediated by integrins receptor on the surface of the cells and their binding to vitronectin ligand on the extracellular matrix and for wound healing cell motility is required (p 859, 1st column). Klemke teaches that FG cells expressing the $\alpha v \beta 5$ integrin receptor in the presence of EGF in the medium activate the tyrosine kinase pathway which mediates cell motility and not attachment on the vitronectin ligand in the extracellular matrix in vitro (p 860 2nd column bridge to p 861). **Hocking et al** (JBC, 274(38): 27257-27264, 1999)

teaches that the heparin binding domain of vitronectin inhibits fibronectin matrix assembly (title). Hocking suggests that the heparin binding domain of vitronectin regulates the deposition of fibronectin into the extracellular matrix (abstract). Thus, inherently the integrin $\alpha v \beta 5$ -receptor binding fragment as taught by Klemcke does not comprise a heparin binding domain.

Upton/Vuori/Sommer/Klemcke/Hocking does not specifically teach the IGFBP5 in the culture medium.

However, at the time of the instant invention **Nam et al** (Endocrinology, 143(1): 30–36, 2002) teaches that if vitronectin is incorporated into the ECM, it enhances cellular responsiveness to IGF-I and the addition of IGFBP-5 results in a further enhancement of both cellular migration and DNA synthesis (p 34 1st column). Nam suggests that if vitronectin is incorporated into the ECM there is an increase in the amount of IGFBP-5 that is associated with the ECM. This increased association of IGFBP-5 with ECM proteins results in enhancement of the cellular growth in response to IGF-I (p 34, 1st column). Nam teaches native IGFBP-5 appeared to enhance the cellular migration and DNA synthesis responses to IGF-I for cells plated on plastic or vitronectin, but if cells were plated on a vitronectin enriched matrix the degree of enhancement was increased (p 35, 2nd column, last paragraph).

The combination of prior art cited above in all rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc.* (KSR), 550 U.S. ___, 82 USPQ2d 1385 (2007): “Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a

known device (method, or product) ready for improvement to yield predictable results; (E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

Accordingly, it would have been obvious to the ordinarily skilled artisan to modify the teachings of Upton to utilizing the composition of growth factor IGF-I, an IGFBP3 and vitronectin complex, such as that taught by Vuori and also utilize IGF-II to the complex as taught by Sommer, with a reasonable expectation of success. One of ordinary skill in art would have been motivated to utilize the isolated complex of IGF-I or IGF-II to IGFBP3 and vitronectin into the keratinocyte culture system of Upton since Vuori suggests the pharmaceutical composition comprising IGF and vitronectin promotes wound healing and tissue regeneration (column 2, line 15-29) and particularly since Sommer teaches that a protein complex comprising a native or recombinant IGF and an insulin-like growth factor binding protein (IGFBP) enhances systemic tissue repair and healing in burn injuries (column 5, line 35-42, and line 65 continued through column 6, line 3). Moreover, in view of the teachings of Klemke it would have been prima facie obvious for an ordinary of skill in the art to the vitronectin of Klemke in the culture system in order to activate the tyrosine kinase pathway via the integrin $\alpha v \beta 5$ -receptor resulting in cell motility and preventing binding of the cell on the vitronectin ligand on the extracellular matrix. One of ordinarily skill in the art would have been motivated to modify the teachings of Upton to utilizing IGFBP5 in the culture medium, such as that taught by Nam, with a reasonable

expectation of success. One of ordinary skill in art would have been motivated to use IGFBP5 in the keratinocyte system of Upton in order to augment or diminish binding between IGFs, IGFBPs and vitronectin in vitro with a view to manipulating contingent in vivo biological events associated with cell growth, proliferation and migration are suppressed such as for the purposes of treating wounds prone to hypertrophic scarring such as suggested by Upton. This is further underscored by the teachings of Nam that native IGFBP-5 appeared to enhance the cellular migration and DNA synthesis responses to IGF-I for cells plated on plastic or vitronectin, but if cells were plated on a vitronectin enriched matrix the degree of enhancement was increased (p 35, 2nd column, last paragraph).

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MAGDALENE K. SGAGIAS whose telephone number is (571)272-3305. The examiner can normally be reached on 8.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paras Peter can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair->

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